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COMBINATION OF HYPERTENSIN CONVERTING ENZYME INHIUBITOR WITH A DIURETIC FOR TREATING MICROCIRCULATION DISORDERS [COMBINAISON D'UN INHIBITEUR DE L'ENZYME DE CONVERSION DE L'ANGIOTENSINE ET D'UN DIURETIQUE POUR LE TRAITEMENT DES DESORDRES MICROCIRCULATOIRES]

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The present invention concerns the use of a combination of an /1* angiotensin converting enzyme inhibitor (CEI) and of a diuretic for producing pharmaceutical compositions intended for the treatment of arteriolar-capillary microcirculatory disorders.

It is known that the majority of degenerative vascular diseases, for example arterial hypertension (N.M. Kaplan, *"Microvascular Rarefaction"*, Clinical Hypertension, 6th ed., Baltimore, Wilkinson and Wilkins, 1994, 86; A.S. GREENE et al., *"Microvascular rarefaction and tissue vascular resistance in hypertension"*, Am. J. Physiol., 1989, 256 (Heart Circ. Physiol., 25), H 126-H 31; A.S. IZZARD et al., *"Hypertension and the vasculature: arterioles and the myogenic response"*, J. Hypertens., 1995,13, 1-4; A.M. HEAGERTY et al., *"Small artery structure in hypertension"*, Hypertension, 1993, 21,391-7), but also vascular complications of certain metabolic diseases, for example diabetes mellitus(G. REACH et al., *"Causes et mécanismes de la microangiopathie et de la neuropathie--"L'hypothèse glucose" et ses implications"* [Causes and mechanisms of microangiopathy and neuropathy--"The glucose hypothesis" and its implications]", in: G. Tchobroutsky, G. Slama, R. Assan, P. Freychet, Paris: Pradel, 1990, 448-57), or certain dyslipidemias (J.F. Toole, *"Atherosclerosis"*, Cerebrovascular Disorders, New York, Raven Press, 1984, 199-213) are accompanied by detrimental anatomical and/or functional changes in the arteriolar-capillary microcirculation (J.C.M.L. LE NOBLE et al., "A functional morphometric study of the cremaster muscle microcirculation in young spontaneously hypertensive rats", J. Hypertens., 1990, 8:741-8; I.I.H. CHEN et al., *"Microvascular rarefaction in spontaneously*

*Numbers in the margin indicate pagination in the foreign text.

hypertensive rat cremaster muscle", Am. J. Physiol.,1981, 241:H 306-10).

The detrimental anatomical and/or functional changes in the arteriolar-capillary microcirculation can take different forms, such as, for example:

- arteriolar-capillary rarefaction (P. GASSER, "*Nailfold microcirculation in normotensive and essential hypertensive subjects as assessed by video-microscopy*", J. Hypertens., 1992, 1:83-6),
- lack of arteriolar-capillary recruitment (B.W. ZWEIFACH, "*Micropressure-flow relationships in a skeletal muscle of spontaneously hypertensive rats*", Hypertension, 1981, 3:601-14), /2
- and, more generally, poor adjustment of the distribution of the blood in the tissues as a function of metabolic requirements, any detrimental change capable of inducing or perpetuating tissue hypoperfusion, absolute or relative ischemia, absolute or relative (E. VICAUT, "*Hypertension and the microcirculation: a brief overview of experimental studies*", J. Hypertens., 1992, 10, suppl.5:S59-S68).

It is also known that the anatomical and/or functional alterations in the arteriolar-capillary microcirculation described above can precede, for example, the rise in pressure values in arterial hypertension, creating for some a true vicious circle (A.J. ZWEIFLER et al., "*Diminished finger pulse in borderline hypertension: evidence for early structural vascular abnormality*", Am. Heart J., 1982, 104, 812-15; J.M. SULLIVAN et al., "*Attenuation of the microcirculation in young patients with high-output borderline hypertension*", Hypertension, 1983, 5:844-51).

Finally, it is known that a great many factors are involved

simultaneously in the regulation of general hemodynamics (outputs, resistances, pressures, ...) and in the regulation, or rather adjustment, of the distribution of blood in the tissues as a function of the context (hierarchization depending on the nature of the organs, ...) and the metabolic requirements of the moment (M.J. Mulvany, "The structure of the resistance vasculature in essential hypertension", J. Hypertens.,1987, 5:129:H; H.A.J. STRUIJKER-BOUDIER et al., "*The microcirculation and hypertension*", J. Hypertens., 1992, 10 (suppl. 7):S147-S156).

Very numerous vaso-active substances have been identified, with very particular interest in recent years in, for example, substances originating from or having an effect on smooth muscle fibers and the vascular endothelium (S. LAURENT et al., "*Physiopathologie et pharmacologie du remodelage artériel dans l'hypertension artérielle* [Physiopathology and pharmacology of arterial remodeling in arterial hypertension]", La lettre du pharmacologue, 1997, 11:146-54; TADDEI et al., "*Hypertension causes prematurate aging of endothelial function in humans*", Hypertension, 1997, 29:736-43).

The complexity of these different regulations, the number of factors involved and their interactivity, better understood today, have led us to propose the combination of several directly or indirectly vaso-active medications, for at the same time preventing and treating:

- on the one hand, clinical attack, for example arterial hypertension, when the rise in pressure values reaches, or indeed exceeds, the standards recommended by the international scientific community; /3

- on the other hand, its repercussions on tissue perfusion in the context of macro/microcirculatory disorders which, it is known, can precede, maintain, and aggravate the clinical entity described above ass an example (arterial hypertension but also, for example, vascular complications of certain metabolic diseases...) (H.A.J. STRUIJKER-BOUDIER et al., "*Assessment of the microcirculation in cardiovascular disease*", Clin. Sci., 1996, 91:131-9).

The actions of different vaso-active substances can thus usefully complement one another and provide an improved therapeutic effect for the basic treatment of degenerative vascular diseases, or for the prevention of the incidents and accidents which they induce.

It is also known that some CEI's have a beneficial effect on arteriolar or coronary microcirculation, but at no time has a beneficial effect on the functional unit that an arteriole and the adjacent capillaries represent been demonstrated in the literature.

It has now been shown, which is the subject of the present invention, that the combination of a CEI with a diuretic, in addition to the known properties of this combination, makes it possible, surprisingly, to correct microcirculatory disorders at the arteriolar and capillary level at the same time, although no property of this kind had ever been described or claimed in prior publications or patents relating, in particular, to combinations of CEI and of diuretics, to CEI's or to diuretics.

In addition, the originality of this type of combination of vaso-active agent lies in the fact, in particular, that each of the constituents of the combination is most often used in low doses, generally lower than those used in each of their first indications.

Therefore the usefulness of this type of combination is that pharmaceutical compositions useful for the treatment of arteriolar-capillary micro-circulatory disorders are produced. Thus these compositions can be used in all pathologies where microcirculatory disorders are involved, such as, for example, degenerative vascular diseases, arterial hypertension, cardiac insufficiency, cerebral /4 ischemia, heart attacks, arteritis of the lower limbs, the prevention and treatment of cardiovascular complications of type-II diabetes, retinopathies, nephropathies, etc..., and as main or secondary treatment.

The CEI's usable in these compositions are, but are not limited to: Perindopril, Captopril, Enalapril, Lisinopril, Delapril, Fosinopril, Quinapril, Ramipril, Spirapril, Imidapril, Trandolapril, Benazepril, Cilazapril, and Temocapril, and their addition salts having a pharmaceutically acceptable acid or base.

The preferred CEI's are Perindopril, Captopril, Enalapril, Lisinopril, Benazapril, Quinapril, and Delapril, and their salts, and more particularly Perindopril and its salts.

The diuretics that may be used in these compositions are, but are not limited to: Indapamide, Hydrochlorothiazide, Furosemide, Altizide, Trichlormethiazide, Triflumethazide, Bemetizide, Cyclothiazide, Methylclothiazide, Azosemide, Chlorothiazide, Butizide, Bendrofluazide, Cyclopenthiazide, Benzchlortriazide, Polythiazide, Hydroflumethiazide, Benzthiazide, Ethiazide, Penflutazide, Clopamide, Cicletanide, or Piretanide, and their addition salts with a pharmaceutically acceptable acid or base.

The preferred diuretics are Indapamide and Hydrochlorothiazide

and their salts and, more particularly, Indapamide and its salts.

Therefore the invention more preferably concerns the use of a combination of the conversion enzyme inhibitor Perindopril or one of its addition salts having a pharmaceutically acceptable base and of the diuretic Indapamide in order to obtain pharmaceutical compositions intended for the treatment of arteriolar-capillary microcirculatory disorders.

The pharmaceutical compositions according to the invention will be presented in pharmaceutical forms suitable for oral, parenteral, and, in particular, intravenous, per- or trans-cutaneous, nasal, rectal, perlingual, ocular, or respiratory administration, and more specifically tablets, sublingual tablets, capsules, glossettes, lozenges, injectable preparations, aerosols, eye or nose drops, suppositories, creams, ointments, dermal gels, etc...

Oral administration, and the corresponding pharmaceutical /5
compositions permitting instantaneous or delayed release of the active principles, are preferred.

Tablets are the preferred pharmaceutical compositions.

In the pharmaceutical compositions according to the invention, the amounts of CEI and of diuretic are adjusted to the nature of these active principles and their relative proportions thus vary as a function of the active principles.

When the CEI is Perindopril in the tert-butylamine salt form and when the diuretic is Indapamide, these proportions are respectively between 65 and 85% and between 35 and 15% of the total weight of the active principles and preferably between 70 and 80% for the CEI and between 30 and 20% for the diuretic.

The preferred percentages for this combination are 76% of tert-butylamine salt of Perindopril and 24% of Indapamide.

The compositions according to the invention, in addition to the active principles, contain one or more pharmaceutically acceptable vehicles or excipients.

Pharmaceutically acceptable excipients are, but are not limited to binders, diluents, disintegrating agents, stabilizing agents, preservatives, lubricants, fragrances, flavoring agents, or sweeteners.

The posology varies according to the age and weight of the patient, the administration route, or the nature of the therapeutic indication and of the associated treatments. It ranges between 1 and 50 mg according to the nature of the CEI, and between 0.5 and 25 mg according to the nature of the diuretic, taken one or more times per 24 hours.

Examples of pharmaceutical compositions according to the invention. The examples are cited in a non-limiting way.

EXAMPLE 1: Perindopril/Indapamide Tablets /6

Constituents	*Quantity (mg)*
Perindopril, tert-butylamine salt	2
Indapamide	0.625
Hydrophobic colloidal silica	0.25
Lactose	64.175
Magnesium stearate	0.45
Microcrystalline cellulose	22.5
For a tablet ended at	90

EXAMPLE 2:

Constituents	*Quantity (mg)*
Perindopril, tert-butylamine salt	4
Indapamide	1.25
Hydrophobic colloidal silica	0.25
Lactose	61.55

Magnesium stearate	0.45
Microcrystalline cellulose	22.5
For a tablet ended at	90

EXAMPLE 3:

Constituents	*Quantity (mg)*
Captopril	50
Hydrochlorothiazide	25

EXAMPLE 4:

Constituents	*Quantity (mg)*
Enalapril maleate	20
Hydrochlorothiazide	12.5

EXAMPLE 5:

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Constituents	*Quantity (mg)*
Lisinopril	20
Hydrochlorothiazide	12.5

EXAMPLE 6:

Constituents	*Quantity (mg)*
Benazepril hydrochloride	10
Hydrochlorothiazide	12.5

EXAMPLE 7:

Constituents	*Quantity (mg)*
Quinapril hydrochloride	20
Hydrochlorothiazide	12.5

EXAMPLE 8:

Constituents	*Quantity (mg)*
Perindopril, tert-butylamine salt	2
Hydrochlorothiazide	12.5

EXAMPLE 9:

Constituents	*Quantity (mg)*
Perindopril tert-butylamine salt	4
Hydrochlorothiazide	25

EXAMPLE 10:

Constituents	*Quantity (mg)*
Captopril	50
Indapamide	1.25

EXAMPLE 11: /8

Constituents	*Quantity (mg)*
Enalapril maleate	20
Indapamide	1.25

EXAMPLE 12:

Constituents	*Quantity (mg)*
Lisinopril	20
Indapamide	1.25

EXAMPLE 13:

Constituents	*Quantity (mg)*
Benazepril hydrochloride	10
Indapamide	1.25

EXAMPLE 14:

Constituents	*Quantity (mg)*
Quinapril hydrochloride	20
Indapamide	1.25

EXAMPLE 15:

Constituents	*Quantity (mg)*
Perindopril tert-butylamine salt	4
Bendrofluazide 5	5

EXAMPLE 16:

Constituents	*Quantity (mg)*
Delapril hydrochloride	50
Bendrofluazide	5

EXAMPLE 17: /9

Constituents	*Quantity (mg)*
Delapril hydrochloride	30
Inadapamide	2.5

EXAMPLE 18:

Constituents	*Quantity (mg)*
Delapril hydrochloride	30
Hydrochlorothiazide	25

EXAMPLE 19:

Constituents	*Quantity (mg)*
Fosinopril	10
Hydrochlorothiazide	25

Pharmacological Study of Compositions According to the Invention

Effects of the combination of the tert-butylamine salt of Perindopril (0.76 mg/kg/d, PO)+Indapamide (0.24 mg/kg/d, PO) on the 1R-1C reno-vascular hypertensive rat: Hemodynamic aspect and studies of the sub-endocardial arteriolar-capillary density.

Wistar rats aged 8 weeks (n=56; body weight=200 g) were first subjected to placing a clip (0.2 mm in diameter) on the left renal artery and, four days later, a contralateral nephrectomy was performed. A series of identical rats (n=13) was subjected to the same interventions (anesthesia + surgery) but without stenosis of the renal artery or nephrectomy (NT control group). 1R-1C Goldblatt rats received:

- either a normal diet: HT control group;
- or a diet containing tert-butylamine salt of perindopril (0.76 mg/kg/day) and indapamide (0.24 mg/kg/day): HT group + combination.

The sizes of each group were adjusted, taking into account the specific mortality in each group, so as to be able to analyze, after 4

weeks of treatment, at least 9 animals per group.

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	Numbers operated upon	*Analyzed (survivors)*
NT control	13	13
HT control	21	9
HT + Perindopril-Indapamide combination	18	10

After 4 weeks of treatment, the hemodynamic parameters were recorded under anesthesia (Table I), then the heart was removed for quantitative histomorphometric analysis. The Perindopril salt-Indapamide combination significantly decreased the arterial pressure ($p<0.01$). The cardiac output and heart rate were not modified by the treatment. The degree of left ventricular hypertrophy (LV weight/body weight) was significantly decreased with respect to the HT control group ($p<0.001$).

Table I

	NT control	*HT control*	*HT + combination*
Systolic arterial pressures (mm Hg)	138∀5	209∀12	110∀19
Diastolic arterial pressures (mm Hg)	110∀5	146∀11	79∀12
Cardiac output (ml/min)	59∀4	45∀4	63∀7
Heart rate(/min)	486∀10	455∀19	496∀11
VG weight/body weight (mg/g)	2.1∀0.1	3.7∀0.2	2.2∀0.2

Sub-endocardial capillary density in the wall of the left ventricle

The capillary density was significantly decreased in the HT control group with respect to the NT control group ($p<0.05$) and normalized by the Perindopril salt-Indapamide combination.

Sub-endocardial arteriolar density in the wall of the left ventricle

The number of arterioles per mm^2 of sub-endocardial surface was

significantly increased in the HT control group ($p<0.05$) and normalized in the Perindopril salt-Indapamide combination group.

The results are presented in Table II. /11

Table II

(n/mm²)	*NT control*	*HT control*	*HT + combination*
Sub-endocardial capillary density	1030∀42	916∀39	1076∀41
Sub-endocardial arteriolar density	8.25∀0.46	10.51∀0.41	8.96∀0.63

Therefore the preceding data may be interpreted in the following way:

- It is confirmed that there are detrimental anatomical and/or functional changes in the arteriolar-capillary microcirculation in the majority of degenerative vascular diseases, here in arterial hypertension.
- In the experiment performed here, the most marked anomaly concerns the capillary density, greatly decreased in the hypertensive subjects, and normalized under the effect of the "treatment" by the combination of these two active principles.
- The respective part of the effect of each of the constituents of the combination on the arterioles and the capillaries is, having taken account of the conditions of performing the experiment, difficult to define. However, it seems that each of the constituents has a role on the arteriolar component and the capillary component of the microcirculatory functional unit at the same time.

In conclusion, the fact of combining the Perindopril salt and Indapamide, in the proportions 76/24%, normalizes the sub-endocardial capillary and arteriolar densities studied here in order to illustrate the invention.

CLAIMS

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1. Use of a combination of an angiotensin-converting enzyme inhibitor and a diuretic for producing pharmaceutical combinations intended for the treatment of arteriolar-capillary microcirculatory disorders.

2. The use according to Claim 1, wherein the converting enzyme inhibitor is Perindopril, Captopril, Enalapril, Lisinopril, Delapril, Fosinopril, Quinapril, Ramipril, Spirapril, Imidapril, Trandolapril, Benazepril, Cilazapril, or Temocapril, and the diuretic is Indapamide, Hydrochlorothiazide, Furosemide, Altizide, Trichlormethiazide, Triflumethazide, Bemetizide, Cyclothiazide, Methylclothiazide, Azosemide, Chlorothiazide, Butizide, Bendrofluazide, Cyclopenthiazide, Benzchlortriazide, Polythiazide, Hydroflumethiazide, Benzthiazide, Ethiazide, Penflutazide, Clopamide, Cicletanide, or Piretanide, as well as the addition salts of these compounds with a pharmaceutically acceptable acid or base.

3. The use according to Claim 2, wherein the converting enzyme inhibitor is Perindopril, Captopril, Enalapril, Lisinopril, Benazepril, Quinapril, or Delapril, and the diuretic is Indapamide or Hydrochlorothiazide, as well as addition salts of these compounds with a pharmaceutically acceptable acid or base.

4. The use of a combination of the converting enzyme inhibitor Perindopril or of one of its addition salts with a pharmaceutically acceptable base and the diuretic Indapamide for producing pharmaceutical compositions intended for the treatment of arteriolar-capillary microcirculatory disorders.

5. The use according to Claim 4, wherein the converting enzyme

inhibitor is the tert-butylamine salt of Perindopril and the diuretic is Indapamide.

6. The method according to Claim 4, wherein the pharmaceutical /13 compositions include amounts of tert-butylamine salt of Perindopril and Indapamide respectively between 65 and 85% and between 35 and 15% of the total mass of the active principles.

7. The use according to Claim 6, wherein these amounts are 76% of the tert-butylamine salt of Perindopril and 24% of Indapamide.

8. The method according to Claim 1, wherein the pharmaceutical compositions are in tablet form.

9. The method according to Claim 4, wherein the pharmaceutical compositions are in the form of tablets.

10. A pharmaceutical composition suitable for use according to Claim 9, wherein the tablet contains 2 mg of tert-butyl amine of Perindopril and 0.625 mg of Indapamide as well as excipients or pharmaceutically acceptable non-toxic inert vehicles.

11. A pharmaceutical composition suitable for use according to Claim 9, wherein the tablet contains 4 mg of tert-butylamine salt of Perindopril and 1.25 of Indapamide as well as excipients of pharmaceutically acceptable non-toxic inert vehicles.